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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <p>(21) International Application Number: PCT/GB91/01960</p> <p>(22) International Filing Date: 7 November 1991 (07.11.91)</p> <p>(30) Priority data: 9024365.0 9 November 1990 (09.11.90) GB</p> <p>(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): TAYLOR, Anthony, James [GB/GB]; BURNELL, Patricia, Kwong, Phieu [GB/GB]; Glaxo Group Research Limited, Park Road, Ware, Hertfordshire SG12 0DG (GB).</p> | <p>(74) Agents: FILLER, Wendy, Anne et al.; Glaxo Holdings plc, Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).</p> <p>(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU⁺, TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published With international search report.</p> | |
| (54) Title: AEROSOL MEDICAMENTS | | |
| (57) Abstract | | |
| <p>Aerosol formulations comprising: (A) a medicament in particulate form and having a surface coating of a surfactant; (B) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant; and (C) a cosolvent having higher polarity than the propellant which cosolvent is present in an amount of up to 5 % w/w based upon propellant; and methods for their preparation.</p> | | |

+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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Aerosol medicaments

This invention relates to aerosol formulations of use in the administration of medicaments by inhalation.

The use of aerosols to administer medicaments has been known for several decades. Such aerosols generally comprise the medicament, one or more chlorofluorocarbon propellants and either a surfactant or a solvent, such as ethanol.

The most commonly used aerosol propellants for medicaments have been Freon 11 (CCl_3F) in admixture with Freon 12 (CCl_2F_2) and Freon 114 ($\text{CF}_2\text{Cl.CF}_2\text{Cl}$). However these propellants are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants.

A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise hydrogen-containing chlorofluorocarbons and fluorocarbons; medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777. EP 0372777 requires the use of 1,1,1,2-tetrafluoroethane in combination with both a cosolvent having greater polarity than 1,1,1,2-tetrafluoroethane (e.g. an alcohol or a lower alkane) and a surfactant in order to achieve a stable formulation of a medicament powder. In particular it is noted in the specification at page 3, line 7 that "it has been found that the use of Propellant 134a (1,1,1,2-tetrafluoroethane) and drug as a binary mixture or in combination with a conventional surfactant such as sorbitan trioleate does not provide formulations having suitable properties for use with pressurised inhalers".

We have now surprisingly found that, in contradistinction to this teaching, it is in fact possible to obtain stable dispersions of finely-powdered medicaments together with surfactants in hydrogen-containing fluorocarbon or chlorofluorocarbon propellants such as 1,1,1,2-tetrafluoroethane if the surfactant is present as a dry coating on the particles of medicament and that the stability of the resulting dispersion is enhanced by the presence of small

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quantities (e.g. up to 5% w/w) of cosolvents having higher polarity than the propellant such as lower alkanols (e.g. ethanol). This is in contrast to the procedure of EP 0372777, where the medicament and surfactant are simultaneously homogenised, e.g. in ethanol, prior to addition of the propellant.

There is thus provided an aerosol formulation comprising:-

(A) a medicament in particulate form and having a surface coating of a surfactant;

(B) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant; and

(C) a cosolvent having higher polarity than the propellant which cosolvent is present in an amount of up to 5% w/w based upon propellant.

The propellants for use in the invention may be any hydrogen-containing fluorocarbon or chlorofluorocarbon or mixtures thereof having a sufficient vapour pressure to render them effective as propellants. Such propellants include for example C_{1-4} hydrogen-containing fluorocarbons and chlorofluorocarbons such as CH_2ClF , $CClF_2-CHClF$, $CF_3-CHClF$, CHF_2-CClF_2 , $CHClF-CHF_2$, CF_3-CH_2Cl , CHF_2-CHF_2 , CF_3-CH_2F , $CClF_2-CH_3$, CHF_2-CH_3 and CF_3CHFCF_3 .

Where mixtures of the hydrogen-containing fluorocarbons or chlorofluorocarbons are employed they may be mixtures of the above identified compounds or mixtures, preferably binary mixtures, with other hydrogen-containing fluorocarbons or chlorofluorocarbons for example $CHClF_2$, CH_2F_2 and CF_3CH_3 .

The propellant may additionally contain a volatile saturated hydrocarbon for example n-butane, isobutane, pentane and isopentane. Preferably a single hydrogen-containing fluorocarbon or chlorofluorocarbon is employed as the propellant. Preferably the propellant will be a non-solvent for the medicament. Particularly preferred as propellants are 1,1,1,2-tetrafluoroethane ($CF_3.CH_2F$) and 1,1,1,2,3,3,3-heptafluoro-n-propane ($CF_3.CHF.CF_3$).

It is desirable that the formulations of the invention contain no components which may provoke the degradation of stratospheric ozone. In particular it is desirable that the formulations are substantially free of chlorofluorocarbons such as CCl_3F , CCl_2F_2 and CF_3CCl_3 .

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Cosolvents which may be used include (e.g. C₂₋₆) aliphatic alcohols and polyols such as ethanol, isopropanol and propylene glycol. Preferably ethanol will be employed. In general only small quantities (e.g. 0.05 - 3.0% w/w) are required to improve the stability of the dispersion - the use of quantities in excess of 5% w/w may tend to dissolve the medicament and/or surfactant. Formulations in accordance with the invention preferably contain less than 1% w/w, e.g. about 0.1% w/w, of cosolvent.

Medicaments which may be administered using aerosol formulations according to the invention include any drugs useful in inhalation therapy which may be presented in a form which is substantially completely insoluble in the selected propellant. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. dilitiazem; antiallergics, e.g. cromolyn; antibiotics, e.g. cephalosporins, penicillins, streptomycin, sulphonamides or tetracyclines; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone, flunisolide or fluticasone; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, epinephrine, isoproterenol, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, rimiterol, salbutamol, salmeterol, (-)-4-amino-3,5-dichloro- α -[[[6-(2-(2-pyridinyl)ethoxy)hexyl]amino] methyl]benzenemethanol or terbutaline; diuretics, e.g. amiloride; hormones, e.g. cortisone, hydrocortisone or prednisolone; and therapeutic proteins and peptides, e.g. glucagon. Where appropriate the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred medicaments for administration using aerosol formulations in accordance with the invention include bronchodilators and anti-inflammatory steroids currently used in the treatment of asthma by inhalations therapy. Salbutamol (eg. as the sulphate), salmeterol (e.g. as the hydroxynaphthoate), beclomethasone esters (e.g. the dipropionate) or fluticasone esters

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(e.g. the propionate) are especially preferred medicaments for use in the formulations of the invention.

The surfactants for use in the invention will have no affinity for the propellant (that is to say they will contain no groups which have affinity with the propellant).

The surfactants must be physiologically acceptable upon administration by inhalation. Surfactants within this category include materials such as benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate (Span R 85).

The use of substantially non-ionic surfactants which have reasonable solubility in substantially non-polar solvents is frequently advantageous since it facilitates coating of the medicament particles using solutions of surfactant in non-polar solvents in which the medicament has limited or minimal solubility.

Thus according to a further aspect of the invention the aerosol formulations may be prepared by slurring particulate (e.g. micronised) medicament with a solution of a surfactant such as lecithin in a substantially non-polar solvent (e.g. a lower alkane such as isopentane or a chlorofluorocarbon such as trichlorofluoromethane), optionally homogenising the slurry (e.g. by sonication), removing the solvent and if necessary simultaneously and/or subsequently breaking up the resulting solid cake, and dispersing the thus-obtained surfactant-coated particulate medicament in the chosen propellant in an appropriate aerosol container, e.g. with the aid of sonication. It may be preferred to add the cosolvent after the coated medicament and propellant have been combined, in order to minimise any solubilising effects of the cosolvent and thereby enhance the stability of the dispersion. The process is desirably carried out under anhydrous conditions to obviate hydrate formation.

The particle size of the finely-powdered medicament should be such as to permit inhalation of substantially all of the medicament into the bronchial system upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and preferably in the range 2-10 microns, e.g. 2-5 microns.

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The amount of surfactant employed in coating the particulate medicament is desirably in the range 0.01-10.0% w/w, preferably 0.05-5.0% w/w, relative to the medicament, and may advantageously be chosen such that a substantially monomolecular coating of surfactant is formed. The final aerosol formulation desirably contains 0.005-5.0% w/w, preferably 0.01-1.0% w/w, of coated medicament relative to the total weight of the formulation.

The following non-limitative Examples serve to illustrate the invention.

EXAMPLE 1

(A) Preparation of Lecithin-coated Salmeterol Hydroxynaphthoate

(a) Lecithin (Epikuron 145V - 3.65mg) was dissolved in a small amount of isopentane and the resulting solution was added to micronised salmeterol hydroxynaphthoate (0.5g). Further isopentane (7.0g total) was added to form a slurry, which was sonicated for 3 minutes. The resulting suspension was dried by evaporating the isopentane at ambient temperature in a fume cupboard, whereafter the resulting dried plug was roughly broken up and then dried further in a vacuum oven. The thus-obtained product was further broken up using a mortar and pestle to yield lecithin-coated salmeterol hydroxynaphthoate containing 0.73% w/w of lecithin relative to the salmeterol hydroxynaphthoate.

(b) The above procedure was repeated except that 6.10mg of lecithin was employed, whereby a coated product containing 1.22% w/w of lecithin relative to the salmeterol hydroxynaphthoate was obtained.

(c) The above procedure was again repeated except that 7.80mg of lecithin was employed, thereby yielding a coated product containing 1.56% w/w of lecithin relative to the salmeterol hydroxynaphthoate.

(B) Formulation of Lecithin-coated Salmeterol Hydroxynaphthoate in Ethanol-containing 1,1,1,2-Tetrafluoroethane

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(a) Samples of each of the products of Examples 1(A) (a)-(c) (9.1mg) were weighed into aerosol cans containing dried ethanol (0.018g - 0.1% w/w of total fill weight) and 1,1,1,2-tetrafluoroethane (ca. 5g). Further 1,1,1,2-tetrafluoroethane (total 18.2g - 99.95% w/w of total fill weight) was added to each can, whereafter suitable metering valves were crimped onto the cans, which were then each sonicated for 5 minutes. The resulting aerosols contained salmeterol in an amount equivalent to 240 actuations at 25 μ g per actuation.

(b) The above procedure was repeated except that 0.091g of dried ethanol was employed in each formulation, whereby aerosols containing 0.5% w/w ethanol and 99.45% w/w of propellant were obtained.

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Claims

1. An aerosol formulation comprising:-
 - (A) a medicament in particulate form and having a surface coating of a surfactant;
 - (B) a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant; and
 - (C) a cosolvent having higher polarity than the propellant which cosolvent is present in an amount of up to 5% w/w based upon propellant.
2. A formulation as claimed in claim 1 wherein the propellant comprises 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane.
3. A formulation as claimed in claim 1 wherein the propellant comprises 1,1,1,2-tetrafluoroethane.
4. A formulation as claimed in any one of claims 1 to 3 which is substantially free of chlorofluorocarbons.
5. A formulation as claimed in any one of claims 1 to 4 wherein the cosolvent is selected from an aliphatic alcohol or a polyol.
6. A formulation as claimed in any one of claims 1 to 5 wherein the coated medicament has a particle size of less than 100 microns.
7. A formulation as claimed in any one of claims 1 to 6 wherein the surfactant is present in an amount of from 0.01 to 10% w/w based on the medicament.

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8. A formulation as claimed in any one of claims 1 to 7 wherein the surfactant is selected from benzalkonium chloride, lecithin, oleic acid and sorbitan trioleate.
9. A formulation as claimed in any one of claims 1 to 8 wherein the surfactant-coated medicament is present in an amount of 0.005-5% w/w based upon the total weight of the medicament.
10. A formulation as claimed in any one of claims 1 to 9 wherein the medicament is selected from salbutamol, salmeterol, beclomethasone esters or fluticasone esters.
11. A method for the preparation of an aerosol formulation comprising dispersing a surface-coated medicament in a hydrogen-containing fluorocarbon or chlorofluorocarbon propellant in an aerosol container and then adding the cosolvent.
12. A method as claimed in claim 11 wherein the surface-coated medicament is obtained by slurrying particulate medicament with a solution of a surfactant in a substantially non-polar solvent and then removing the solvent.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 91/01960

| I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 9/12 A 61 K 9/72 | | | | | | | | | | | | | | |
|---|--|-------------------------------------|--|--|--|--|--|------|---|---|------|-----|--|------|
| II. FIELDS SEARCHED <div style="text-align: center; border: 1px solid black; padding: 2px;">Minimum Documentation Searched⁷</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; padding: 5px;">Classification System</td> <td style="padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="padding: 5px;">Int.C1.5</td> <td style="padding: 5px;">A 61 K</td> </tr> </table> <div style="text-align: center; padding: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched⁸</div> | | | Classification System | Classification Symbols | Int.C1.5 | A 61 K | | | | | | | | |
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| III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category *</th> <th style="width: 70%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; padding: 5px;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">US,A,4352789 (C.G. THIEL) 5 October 1982, see the claims 1-5,11-13,15-17; column 5, lines 17-24; column 6, lines 8-15 -----</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-12</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;">EP,A,0372777 (RIKER) 13 June 1990, see the claims 1-2,5-6,10-13 (cited in the application) -----</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-12</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">P,Y</td> <td style="padding: 5px;">WO,A,9104011 (RIKER) 4 April 1991, see the claims -----</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1-12</td> </tr> </tbody> </table> | | | Category * | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | Y | US,A,4352789 (C.G. THIEL) 5 October 1982, see the claims 1-5,11-13,15-17; column 5, lines 17-24; column 6, lines 8-15 ----- | 1-12 | Y | EP,A,0372777 (RIKER) 13 June 1990, see the claims 1-2,5-6,10-13 (cited in the application) ----- | 1-12 | P,Y | WO,A,9104011 (RIKER) 4 April 1991, see the claims ----- | 1-12 |
| Category * | Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹² | Relevant to Claim No. ¹³ | | | | | | | | | | | | |
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| P,Y | WO,A,9104011 (RIKER) 4 April 1991, see the claims ----- | 1-12 | | | | | | | | | | | | |
| <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>^{"A"} document defining the general state of the art which is not considered to be of particular relevance</p> <p>^{"E"} earlier document but published on or after the international filing date</p> <p>^{"T"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>^{"O"} document referring to an oral disclosure, use, exhibition or other means</p> <p>^{"P"} document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 50%;"> <p>^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>^{"X"} document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>^{"Y"} document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>^{"A"} document member of the same patent family</p> </div> </div> | | | | | | | | | | | | | | |
| IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center;">18-12-1991</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center;">- 9. 01. 92</div> </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; padding: 2px; margin-right: 10px;">M. PEIS</div> <div style="font-family: cursive; font-size: 1.2em;">M. Peis</div> </div> </td> </tr> </table> | | | Date of the Actual Completion of the International Search <div style="text-align: center;">18-12-1991</div> | Date of Mailing of this International Search Report <div style="text-align: center;">- 9. 01. 92</div> | International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> | Signature of Authorized Officer <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; padding: 2px; margin-right: 10px;">M. PEIS</div> <div style="font-family: cursive; font-size: 1.2em;">M. Peis</div> </div> | | | | | | | | |
| Date of the Actual Completion of the International Search <div style="text-align: center;">18-12-1991</div> | Date of Mailing of this International Search Report <div style="text-align: center;">- 9. 01. 92</div> | | | | | | | | | | | | | |
| International Searching Authority <div style="text-align: center;">EUROPEAN PATENT OFFICE</div> | Signature of Authorized Officer <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; padding: 2px; margin-right: 10px;">M. PEIS</div> <div style="font-family: cursive; font-size: 1.2em;">M. Peis</div> </div> | | | | | | | | | | | | | |

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
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GB 9101960

SA 53071

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| US-A- 4352789 | 05-10-82 | None | |
| EP-A- 0372777 | 13-06-90 | AU-A- 4595689 | 14-06-90 |
| | | CA-A- 2004598 | 06-06-90 |
| | | JP-A- 2200627 | 08-08-90 |
| WO-A- 9104011 | 04-04-91 | AU-A- 6409790 | 18-04-91 |

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